ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

KidneyNews

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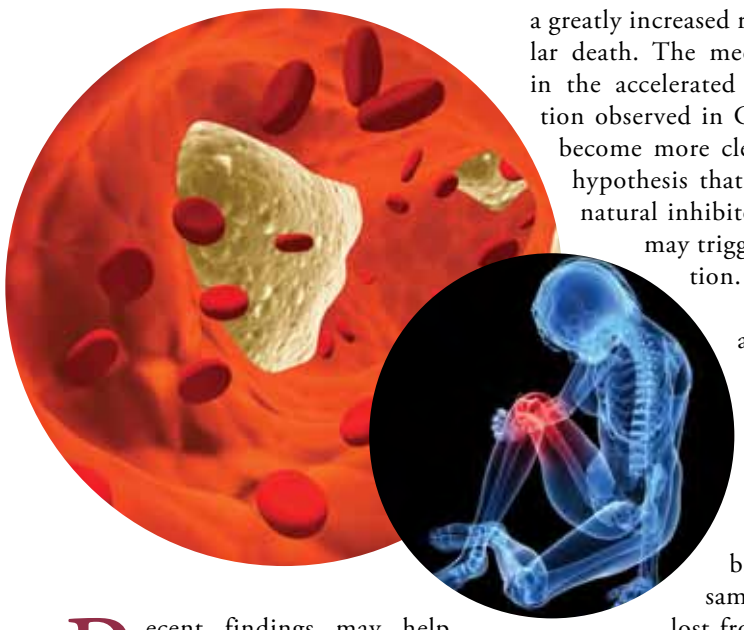
The Calcium Paradox Revisited

By Julie Taylor



Recent findings may help explain the calcium paradox—the relationship between osteoporosis and atherosclerosis—that plays a large role in aging and is a particular concern in those with chronic kidney disease (CKD).

Patients with CKD have a higher incidence of vascular calcification and a greatly increased risk of cardiovascular death. The mechanisms involved in the accelerated vascular calcification observed in CKD have recently become more clear, leading to the hypothesis that perhaps a lack of natural inhibitors of calcification may trigger calcium deposition.

Aging can be seen as a process of calcification, the literal ossification of the body's tissues—including the arteries, heart, kidney, and brain—while at the same time calcium is lost from bone, resulting in thinning and fracturing of the bones, or osteoporosis.

Osteoporosis results when the body removes more bone than it replaces. Calcification outside the bone tissue is due to the body's regulators of calcium metabolism becoming less efficient as aging progresses.

A recent study looked at the progression of aortic calcification in chronic dialysis patients with disorders of mineral metabolism (*Nephrol Dial Transplant* 2011; 5:1747–8).

"Aortic calcification progressed in almost a third of the patients during dialysis," said Marlies Noordzil of the department of clinical epidemiology at the University of Amsterdam. "Hypercalcemia and hyperparathyroidism were associated with an increased risk of progression."

It's well known that Vitamin D3 and vitamin K-complex, as well as magnesium, help normalize the efficiency of calcium metabolism ensuring proper calcification of bone tissue while preventing pathological calcification of the vascular and organ systems. These vitamins work synergistically to keep calcium where it belongs.

Much has been written about vitamin D recently and the "monitoring and maintenance of vitamin levels throughout the stages of CKD" said Eleanor Lederer, professor of medi-

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Hepatitis C Infection with HIV Raises Risk of Chronic Kidney Disease

Chronic hepatitis C virus (HCV) infection raises the risk for chronic kidney disease (CKD) in people infected with human immunodeficiency virus (HIV). Clearing the HCV infection appears to reverse this effect, researchers have found.

"In this whole era of treatability of HIV [and] the aging patient, it becomes of much bigger concern what other target organ damage are we going to see," Jürgen Rockstroh, MD, told *ASN Kidney News* at the 13th European AIDS Conference in Belgrade, Serbia, late last year. Rockstroh is professor of medicine and head of the HIV clinic in the department of medicine at the University of Bonn in Bonn, Germany.

"In several observations we've seen there has been an independent association between hepatitis C co-infection and risk for development of chronic kidney disease," Rockstroh said.

In the United States, about 25 percent of individuals infected with HIV are also infected with HCV. The rate among injection drug users is much higher. About 80 percent of users with HIV are also infected with HCV, according to the U.S. Centers for Disease Control and Prevention.

Using the prospective, observational

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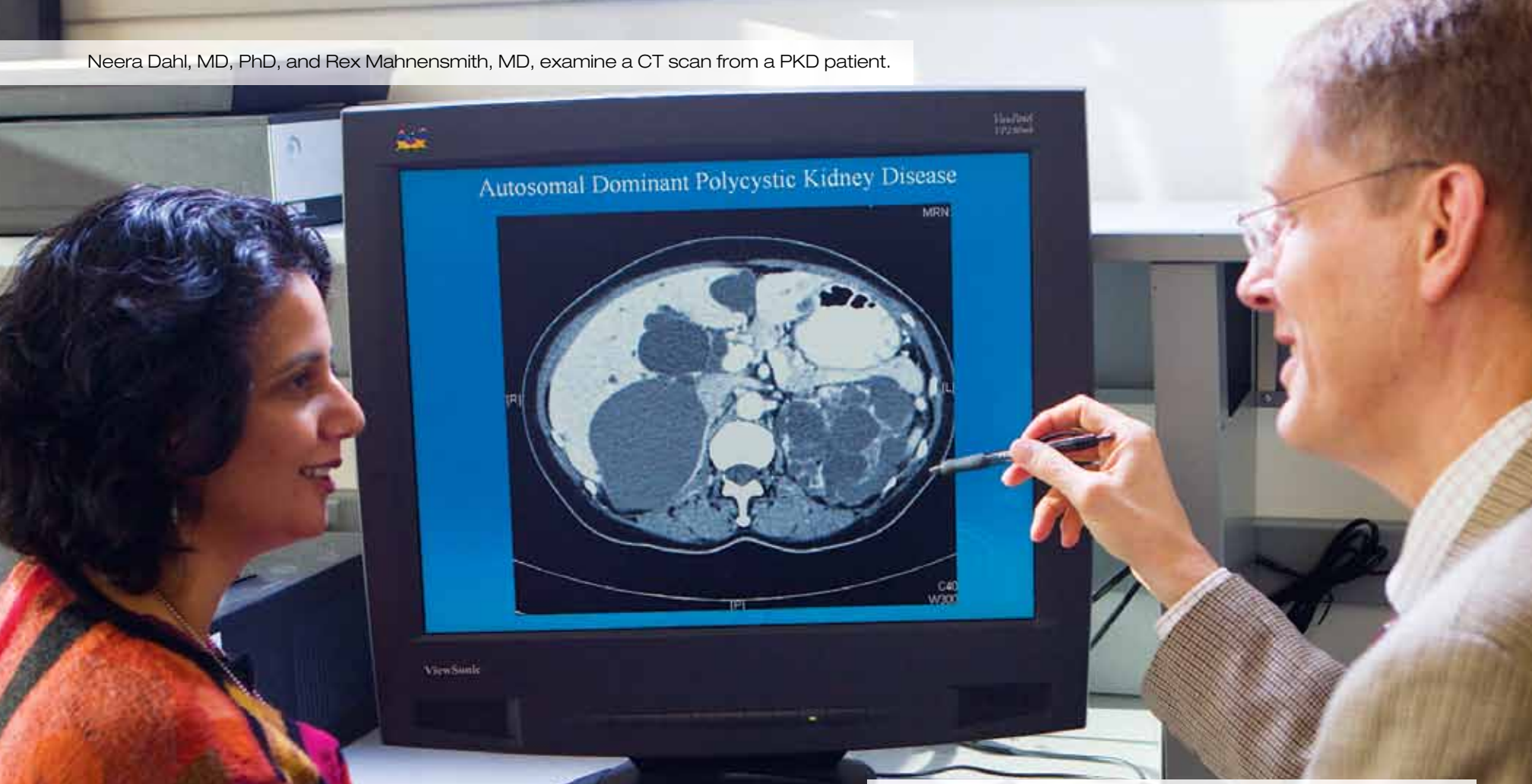
Inside

Neera Dahl, MD, PhD, and Rex Mahnensmith, MD, examine a CT scan from a PKD patient.



Research Excellence, Clinical Leadership and a Commitment to Our Patients

Yale-New Haven Hospital is the primary teaching hospital of Yale School of Medicine. Nephrology services at Yale-New Haven were ranked 35th by *U.S.News & World Report* in 2011-12.

The genetics behind kidney disease are intricate and multi-faceted. Only a few medical institutions in the country have the commitment to understanding and treating inherited kidney diseases and the resources to house the prestigious George M. O'Brien Kidney Research Center and a Polycystic Kidney Disease (PKD) Research Center, all supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). We are one of those centers.

Our researchers have discovered over fifteen genes for human diseases affecting the kidney and blood pressure. These discoveries cover the gamut from rare disorders of blood pressure regulation through sodium and potassium handling such as Liddle's syndrome, pseudohypoaldosteronism type II and Bartter's and Gittelman's syndromes to such common inherited kidney diseases as polycystic kidney disease (PKD). While our researchers are now seeking to translate these findings to treatments for PKD and other disorders, our nephrologists are using these discoveries to help our patients lead healthy and fulfilling lives.

Being at the forefront of clinical research and treatments means that our physicians and surgeons are furthering the current understanding of kidney disease. Most importantly, it means they are positioned to provide the best care possible to our patients.

Yale-New Haven Hospital

www.ynhh.org

Calcium Paradox

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cine, Robley Rex VA Medical Center and University of Louisville School of Medicine in Louisville, KY. "A fall in 1,25 hydroxyvitamin D is the first measurable change in mineral metabolism noted during the course of CKD, long before the onset of hyperparathyroidism, hyperphosphatemia, or hypocalcemia. The nearly universal prevalence of bone mineral disorders in this population suggests strongly the need for vitamin D replacement."

In December of 2010, the Institute of Medicine (IOM) raised the Recommended Daily Allowance (RDA) of vitamin D for young adults from 200 IU (International Units) to 600 IU while the RDA for people over 70 was raised to 800 IU.

Vitamin D3 is a vital cofactor in both bone mineralization and calcium absorption in the intestines. When synthesized in the kidneys, the vitamin is released into the circulation and acts as a hormone, regulating (among other things) the concentration of calcium and phosphate in the bloodstream, promoting the healthy mineralization, growth, and remodeling of bone tissue. It does this by binding to vitamin D-binding protein (VDR). The binding of vitamin D3 to the VDR acts as a transcription factor that modulates gene expression of transport proteins such as TRPV6 and calcindin, which are involved in calcium absorption in the intestine.

Vitamin D also acts to inhibit vascular calcification by blocking the release of fat-derived inflammatory cytokines that contribute to both inflammation and adhesion in the arteries and elsewhere. These cytokines play a role in atherosclerosis and osteoporosis. Several inflammatory cytokines are induced by oxidative stress, and are a factor in chronic inflammation.

Also taking center stage for its role in mediating calcium regulation is Vitamin K. Research shows that without adequate vitamin K to meditate this process, calcium saturates the arterial walls and other soft tissues. It appears that vitamin K deficiency helps to explain the "calcium paradox"—the apparent relationship between osteoporosis and atheroscelosis.

The discovery that blood vessel cells can transform into bone-forming cells confirmed this link. While low vitamin D is linked with arterial disease and osteoporosis, vitamin K's role is to stimulate bone formation and modify specific Gla proteins that prevent calcification outside of bone tissue.

How does Vitamin K help prevent calcification outside of bone? It acts as a co-factor required to convert the amino acid glutamate into one of about 15 human proteins with Gla domains, including matrix Gla protein (MGP).

MGP is a vitamin K–dependent protein secreted in cartilage, lung, heart, kidney, and arteries. While the precise mechanism of action is not completely understood, it is generally accepted that MGP is a strong inhibitor of soft tissue calcification.

In the April 2010 issue of the *Clinical Journal of the American Society of Nephrology,* Leon Schurgers noted that "Vitamin K–dependent MGP acts as a calcification inhibitor," and that, "levels of the inactive, dephosphorylated, uncarboxylated MGP (dp-uc MGP) increased progressively in a CKD setting, and thus could be a marker for vascular calcification in CKD."

Noting that "the majority of dialysis patients exhibit pronounced vitamin K deficiency," the authors of a February 2011 *Journal of the American Society of Nephrology* article said that more study needs to be done to see whether vitamin K supplementation improves outcomes in hemodialysis patients. The article, "Circulating nonphosphorylated carboxylated gla protein predicts survival in ESRD," was jointly authored under G.Schlieper of the Department of Nephrology and Clinical Immunolgy, Rheinishe -Westfalishe Technische, in Aachen, Germany.

Know your Vitamin K: Some Forms Protect Heart and Kidneys More than Others

By Leon Schurgers

Vitamin K has long been regarded solely as a coagulation co-factor, thus the name "the coagulation vitamin." This concept is now outdated. Vitamin K-dependent proteins have a role outside coagulation.

Vitamin K can be subdivided into vitamin K1 and the menaquinones (vitamin K2). Vitamin K is a family name for a series of compounds that have in common a 2-methyl-1,4-naphthoquinone ring structure but differ in their aliphatic side chain at the 3-position.

Most studies on Vitamin K use either K1 or menaquinone-4 (MK-4). The reason for this is that both synthetic vitamins have been available on the market for many years. Awareness of the beneficial properties of long-chain menaquinones like MK-7 only arose in the last decade. Studies by our group and others showed that long chain menaquinones benefit from great intestinal absorption, a long plasma half-life, and a high bioactivity compared with both K1 and MK-4.

After absorption, all K vitamins are incorporated into chylomicrons and enter the bloodstream, and are then rapidly cleared by the liver. A vitamin K deficiency is therefore very uncommon in the normal population.

A redistribution of K vitamins for extrahepatic tissues occurs in the liver. The hypothesis is that only at hepatic vitamin K sufficiency is vitamin K (notably the long-chain menaquinones) incorporated into LDL and available for extrahepatic tissues. Thus, the first signs of vitamin K insufficiency are seen in bone and vasculature. Indeed, the occurence of PIVKA-II (protein induced by vitamin K-absence II; ucFII) is very rare whereas uncarboxylated osteocalcin and uncarboxylated matrix Gla-proteins are very common in the general population.

In cross-sectional analysis among ~5000 elderly apparently healthy individuals in the Netherlands, we have demonstrated that dietary vitamin K2 intake was inversely associated with vascular calcification and mortality. After adjustment for potential confounders, the cardiovascular mortality in the highest tertile for vitamin K2 intake was 50 percent lower than in the lowest tertile for vitamin K2 intake. Such association was not found for phylloquinone. These results were confirmed in a recent analysis of over 16,000 postmenopausal women. It was found that the forms of vitamin K2 with the highest cardioprotective activity were the long-chain menaquinones MK-7, MK-8, and MK-9. These are the forms found in cheese and curd cheese. In this study, the effect of vitamin K2 was a reduction of cardiovascular disease of 9 percent for every 10 μg of dietary K2.

Longitudinal studies in healthy volunteers and patients suffering from vitamin K deficiency will address whether vitamin K supplementation can inhibit vascular calcification and outcome. A recent pilot study demonstrated that the dose-dependent supplementation of MK-7 in hemodialysis patients resulted in a significant reduction of the circulating inactive form of matrix Gla-protein. Whether the supplementation of vitamin K2 could inhibit vascular calcification and subsequent cardiovascular mortality is the subject of current research.

Leon Schurgers, MD, is with the department of biochemistry, Cardiovascular Research Institute Maastricht, Maastricht, the Netherlands.

Hepatitis CKD Risk

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EuroSIDA international cohort of more than 16,500 HIV-infected patients, investigators found that when compared to HIV-infected people who were negative for HCV antibodies, individuals who were positive for HCV antibodies had a 98 percent increased incidence of CKD.

HCV antibodies indicate exposure to the virus at some point and may persist even if the virus is cleared from the body naturally or by treatment. Viremia, or circulating HCV RNA, indicates an active infection.

Patients eligible for the study had at least three serum creatinine determinations after January 1, 2004. Their HCV antibody status was known. The baseline estimated glomerular filtration rate (eGFR) was the first one recorded, and CKD was defined either as an eGFR less than or equal to 60 mL/min/1.73 m^2 for individuals with baselines above this point, or as a 25 percent decline in eGFR for individuals whose baseline was at or below 60 mL/min/1.73 m^2.

Among 8001 patients, 1964 (24.5 percent) were positive for HCV antibodies. Of these, 972 (49.5 percent) were HCV RNA-positive. At baseline, the median age was 41 years, the median CD4 T cell count was 439 cells/mm^3 (range 294–627), and the median eGFR was 97.6 mL/min/1.73 m^2 (range 83.8–113.0). Progression to CKD occurred in 410 patients (5.1 percent)—an incidence of 13.6 per 1000 person-years of follow up. For those who progressed to CKD these variables were accounted for: cumulative use of nephrotoxic drugs and antiretroviral drugs, CD4 counts and nadirs, age, gender, and diabetes.

Patients with HCV antibodies who had HCV viremia or had unknown HCV RNA status in their blood were at significantly higher risk for CKD. The higher the viral load, the higher the incidence of CKD ($p < 0.04$ for all viral loads greater than 615 IU/mL).

Individuals with antibodies but who had undetectable viral loads (<615 IU/mL) were at no greater risk for CKD compared to patients without HCV antibodies. The incidence of CKD was not associated with the HCV viral genotype.

Rockstroh said it is not known why patients with HCV are at higher risk for the development of CKD.

"One point could be that patients who have chronic hepatitis C obviously will have different stages of liver disease, and in very end stage liver disease you can often have what we call hepatorenal syndrome, so there are perfusion issues with the kidney, and then you can get kidney failure," he speculated. Another contributing factor could be altered drug metabolism by the liver, leading to levels of antiretroviral drugs that may cause renal tubular damage.

A remaining question is whether successful treatment and clearance of HCV can reverse kidney disease. The EuroSIDA database probably has too few successfully treated patients to answer the question since many come from Eastern Europe, where treatment is often not available.

At this point, Rockstroh recommends careful selection of any renal toxic antiretroviral drugs. Beyond that, "we just have to monitor renal function and renal disease parameters more closely in [HIV] patients with hepatitis C in the future," he said.

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Kidney Disease Included in New HIV Treatment Guidelines

Recently released guidelines of the European AIDS Clinical Society for the first time give special emphasis to co-morbidities that may occur in patients infected with HIV. Kidney disease and related conditions figure prominently in the guidelines.

Suppression of HIV has become so effective that co-morbidities are now a real concern, said Jens Lundgren, MD, DMSc, professor in the department of international health, immunology, and microbiology at the University of Copenhagen, director of the Copenhagen HIV Program, and chairman of the section on co-morbidities of the guidelines committee.

"HIV physicians are great in treating the virus but may not have the skill set necessarily to deal with the prevention and treatment of the co-morbidities," Lundgren said. "We have involved experts in the fields of the organ diseases, and therefore we believe that we are providing contemporary guidance on that."

Screening for kidney disease

"It is absolutely clear now that we do need HIV clinics to start to screen the urine for protein in order for you to be able to calculate the urine protein-to-creatinine ratio because this has major impact not only on the progression of the kidney disease but also on extra-renal complications for people with impairment of renal function," Lundgren said. "We can no longer just take blood from patients."

A table in the guidelines helps manage patients according to the estimated glomerular filtration rate and the urinary protein-to-creatinine ratio. Various anti-retroviral drugs can be nephrotoxic, and the guidelines provide a table presenting management strategies in this evolving area.

Noninfectious co-morbidities in HIV

Tables or flow charts lead clinicians through cancer screening, prevention of CVD, diagnosis and management of dyslipidemia, hypertension, and diabetes, and management of kidney disease, bone disease, vitamin D deficiency, and drug-associated nephrotoxicity.

Lundgren said all patients should be scored for their risk of CVD with an HIV-specific risk equation, and one should consider modifying anti-retroviral therapy if the 10-year risk of a cardiovascular event is greater than 20 percent. Lipid-lowering therapy is now recommended only if the 10-year risk is greater than 20 percent in primary prevention. Substantial age and race-based updates to hypertension management have been formulated with the advice of experts in that field.

The panel decided that an appropriate cutoff for the diagnosis of impaired glucose tolerance is a fasting plasma glucose level of 5.7 to 6.9 mmol/L (110 to 125 mg/dL), as recommended by the World Health Organization and the International Diabetes Federation in 2005. It recommended metformin or possibly sulfonylureas for first-line treatment, depending on specific patient characteristics. HIV-specific factors can affect glycated hemoglobin values, so plasma glucose may be a better indicator of the need for treatment. As good practice would dictate, clinicians are urged to screen their diabetic patients for nephropathy, retinopathy, and polyneuropathy.

The guidelines are available at www.europeanaidsclinicalsociety.org in English and 13 additional languages so far.

The web version ultimately will offer additional information, tables, and links to resources on renal tests and drug dosage adjustments for renal impairment, management of metabolic disorders, lifestyle interventions, antidepressant drugs, and activities of daily living. Significant attention is given to adverse effects and drug-drug interactions.

Letters

***ASN Kidney News* accepts letters to the editor in response to published articles. Please submit all correspondence to kidneynews@asn-online.org**

The List: ASN Kidney News "Top to Watch" in 2012

States Wrestle with Health Reform Implementation

States this year will struggle to implement some of the provisions of the Accountable Care Act (ACA) while at the same time keeping an eye on efforts to repeal several of the provisions. Major reforms are set to roll out in 2014.

The Supreme Court announced in November 2011 that it would consider a lawsuit brought by 26 state governments challenging the constitutionality of both the individual mandate and Medicaid expansion. Although a decision could come as early as this summer, the court may have to defer a ruling on the individual mandate until it has run for a year. Based on a federal statute, consumers are barred from challenging a tax law until it has gone into effect and taxes have been paid.

In the meantime, all but seven states are somewhere in the process of creating a health insurance exchange, with 13 states having established an exchange either by state legislation or executive order. Twenty-three states have received federal funding but continue to study their options. Eight have so far been unable to pass legislation. State governments with strong opposition to exchanges may wait for a Supreme Court judgment before taking legislative action. But they risk cutting it close to the January 2013 deadline to determine whether they will run their own exchange or have the federal government take control.

The Institute of Medicine (IOM) recently released a consensus statement, requested by the Secretary of Health and Human Services, outlining criteria and methods to be used in the process of determining an "essential health benefit" (EHB) package as required by the ACA for state health exchanges.

All plans offered through health insurance exchanges must include the EHB package at a minimum, which is based on 10 categories, including hospital services, prescription drugs, preventive services, and maternity care. The IOM emphasized that developing this benefits package will require a delicate balance between providing needed health services and maintaining plan affordability to avoid an explosion in consumer use of subsidized and public health care programs.

Armed with a set of criteria and a preferred methodology for determining benefits from the IOM committee, the Department of Health and Human Services is expected to release EHB rules in 2012, although there is no set deadline. Coverage for dialysis treatments and immunosuppressives for transplant recipients is unclear. Policy analysts must be ready to comb through the rules to be sure these populations are accounted for. Stay tuned.

States will be responsible for ensuring that plans maintain EHB, and may have to decide whether to impose coverage requirements on private plans that may no longer provide services previously required under state law.

To see where your state stands with a health exchange, visit: http://healthreform.kff.org/the-states.aspx

Another ACA provision on the states' radar is the medical loss ratio (MLR) rule, which requires insurers to spend at least 80 percent of premium dollars on clinical services and quality improvement or provide rebates to consumers. Rebates for 2011 will roll out to consumers in 2012. Six states have been granted waivers by the Department of Health and Human Services owing to unstable and/or small state insurance markets. Five states have had their waiver requests denied, and seven states have waivers under consideration. The National Association of Insurance Commissioners recently passed, by a slim margin, a resolution expressing concerns with the ruling and urging Congress to increase protections for insurance brokers and agents, signaling that whether for or against, the MLR continues to be a top priority for state insurance commissioners.

On the Medicaid front, the Centers for Medicare and Medicaid Services (CMS) continues to roll out funding opportunities, authorized by provisions in the ACA, to help states manage health care costs and improve health care delivery. Eight states have been awarded grants to participate in the Medicaid Incentives for Chronic Diseases Program, a three-year pilot measuring the effects of direct incentives on consumer participation in preventive care and healthy behaviors.The newly established Center for Medicare and Medicaid Innovation recently announced the Health Care Innovation Challenge as a means to provide funding for groups to design, implement, and test innovative models of health care delivery and payment for the Medicare, Medicaid, and Children's Health Insurance programs. Awards go up to $30 million and states are welcome to apply as separate entities or as part of a collaborative effort with other payers/providers.

Measuring Quality

Throughout 2012, the nephrology community will be focused on how Medicare's new Quality Incentive Program (QIP) affects patient outcomes and practice patterns.

Mandated by the Medicare Improvement for Patients and Providers Act of 2008, the QIP is the only mandatory "pay-for-performance" program in Medicare. The QIP was designed to establish performance standards for dialysis facilities and to adjust payments based on meeting (or not meeting) those standards.

Speaking at Kidney Week, Jeffrey Berns, MD, FASN, described QIP as a "pay for nonperformance" program or P4nP, since facilities will receive a payment deduction of up to 2 percent if certain performance measures are not met. Reductions in years 2012 and 2013 will be based on hemoglobin measures and urea reduction ratio (URR), with several clinical and process measures being added in 2014. Reductions are made based on a complicated scoring system. Data used for reductions in 2012 and 2013 will come from claims filed in 2010 and 2011 respectively, leaving little room for actual quality improvement based on QIP.

Two of the QIP measures are already met by the majority of dialysis facilities: 96 percent have URR ratio of at least 65 percent and 84 percent keep hemoglobin less than 12 mg/dL. The fact that many facilities meet these standards begs the question of whether these measures really address a performance gap, Berns noted. The two measures also were not endorsed by the National Quality Forum, of which Berns holds a seat as the ASN representative. But they were included in the actual mandate for Congress, so by law they must be included.

Daniel Wiener, MD, assistant professor at Tufts University and member of the ASN's Dialysis Advisory Group, noted that what is good for the majority of patients will still not benefit everyone and may even negatively affect a subpopulation of patients. As a case study, Weiner described how one of the 2014 QIP measures (use of AV fistula) may not be the best choice for everyone. For the elderly, physicians must choose carefully among arteriovenous (AV) fistula use versus catheter or AV, he said. Although targets are set at less than 100 percent to help physicians individualize therapies, Weiner said this may not be adequate to allow for adjustment.

The major components of a pay-for-performance program are operationalizing quality and designing incentives followed by communication, implementation, and evaluation, said Rajnish Mehrotra, MD, FASN, chair of the ASN Dialysis Advisory Group and associate professor at UCLA. Mehrotra applied the dimensions of quality outlined in the Institute of Medicine's 2001 report, demonstrating that QIP is making an effort to provide higher quality care by addressing clinical effectiveness (HgB, URR), patient safety (infection reporting), and patient centeredness (patient experience survey), but has not successfully addressed timeliness, efficiency, or equity.

The incentive structure for the QIP is also off kilter, Mehrotra said, using a payment withhold instead of bonuses, and using payment periods far removed from actual performance periods.

Ultimately, many in the kidney community remain optimistic about the use of quality measures in nephrology care, but will continue to advocate in 2012 for appropriate and effective measures that are better aligned with provider care and reimbursement.

Comparative Effectiveness Research

Measuring quality. Comparing effectiveness. Both will be at the fore of nephrology talk this year.

Over $1 billion in funding was appropriated for comparative effectiveness research (CER) through 2009's American Reinvestment and Recovery Act. Research priorities set by the Institute of Medicine declared racial and ethnic health disparities—a prominent issue for nephrology—high on the list. The category "genitourinary systems" was near the bottom of the list, but project areas for grant funding include comparisons of dialysis modalities.

True to its name, CER can be quite effective in research with kidney disease populations, said Wolfgang Winklemeyer, MD, ScD, director of clinical research for Stanford University's Division of Nephrology and chair of the ASN's Comparative Effectiveness Task Force. Randomized clinical trials, seen as the gold standard, have historically excluded chronic kidney disease patients and often do not reflect the "real world" of everyday clinical practice. In contrast, CER methods focus on trials done in normal settings with larger, more diverse populations, and compare a "usual care" group (instead of the typical placebo group) with groups receiving interventions.

Several research projects exemplify the spirit of CER by using clinical or community settings and testing new strategies against usual care, said Ebony Bouleware, MD, associate director for the Welch Center for Prevention, Epidemiology, and Clinical Research at Johns Hopkins. These research projects include a nurse coordinated care model, a computerized drug alert program, and timing of initiation for erythropoiesis-stimulating agent (ESA) treatment in nondialysis chronic kidney disease.

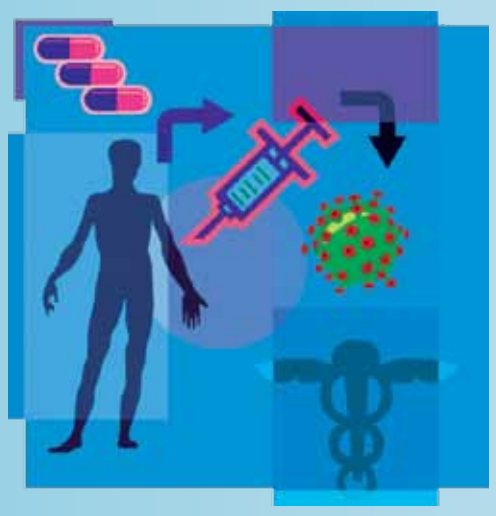
Systematic reviews also fit under the CER umbrella. Steve Brunelli, a nephrologist and renal epidemiologist at Brigham and Women's Hospital, analyzed the past year's many studies focusing on dialysis. Many asked more questions than they answered. This year will likely see more studies designed to clarify best practices for dialysis patients in modality and access choice, timing of treatment initiation, and management of infections and comorbidities.

Watch for news from the Patient-Created Outcomes Research Institute (PCORI) this year. Created through an appropriation in the Affordable Care Act. PCORI is unique in that, although federal monies were appropriated, it acts as a nonprofit, independent entity, led by four committees under a Board of Governors. While not directly funding CER, PCORI will be responsible for improving health care delivery through funding projects that help develop methodologies for CER to ultimately guide patients to make informed decisions based on "high integrity, evidence-based information," said Neil Powe, MD, a member of the Institute of Medicine's (IOM) Committee on CER Prioritization and vice chair of medicine at the University of California San Francisco.

Interest in this type of research is soaring. The first call for proposals in November 2011 received 1400 applicants for 40 available awards. Hopes are high that this new organization will be able to take a focused patient and stakeholder-centered approach to refining, creating, and testing methods that can ultimately be used as practice models for CER.

Winkelmayer, Boulware, Brunelli, and Powe all spoke about CER and its use in nephrology practice during the public policy sessions at Kidney Week 2011.

Gene Therapy: Treating the Transplanted Kidney and Beyond



The goals for gene therapy are becoming both more ambitious and yet more practical as the field matures. The field will show continued advances in 2012.

In one line of research in mice, gene therapy shows promise in delivering agents that cannot be given systemically—either because of side effects or poor pharmacokinetic properties—to reduce chronic transplant dysfunction.

In the early days, researchers envisioned replacing defective genes to completely cure hereditary diseases, efforts that have largely come up short. But meanwhile, less heroic strategies have been progressing, using genes to treat symptoms, or provide short-term therapy rather than a long-term cure.

If there is a near-term role for gene therapy in renal disease, it may be of the latter form, according to Leo Deelman, PhD, assistant professor of medicine at the University of Groningen, the Netherlands. One strategy is to use gene therapy to provide local immune suppression for renal transplantation.

"Transplantation is the first choice for end stage renal disease," Deelman said at Kidney Week 2011, "but it is associated with a lot of problems," including rejection and acute lack of function. Early on, there is ischemia-reperfusion damage, contributing to loss of function and acute rejection. In the long term, nephron loss, inflammation, and fibrosis may occur, leading to chronic failure. "There are also side effects of systemic immunosuppressant therapy. Toxicity is a big problem."

"Gene transfer could help, if we selectively express immunosuppressant molecules in the kidney to prevent rejection," Deelman said.

Delivery of the gene to the target organ has always been a major stumbling block for gene therapy, and so the transplanted kidney is, in some ways, an ideal gene therapy target, since it can be treated in isolation before implantation.

There are multiple potential gene vectors, ranging from whole cells to viruses to naked DNA plasmids. "We thought adenovirus would be the most suitable vector for us," Deelman said, "because it binds to its receptor at low temperatures, meaning that even when you have the transplanted kidney on ice, you could load it with adenovirus, and still get good transfection."

The problem he encountered is that the kidney is relatively poorly stocked with the cellular receptors that the virus binds to to enter the cell. The solution, he found, was to modify the virus so that it binds to another receptor that is plentiful on kidney cells, increasing its uptake.

In an initial study meant to explore the potential of the gene transfer system, Deelman worked with mice in which the donor and recipient were the same strain, to minimize acute rejection. A kidney from the donor was removed and placed on ice, and then perfused with solution containing the virus, which carried a reporter gene. After 20 minutes, the kidney was washed with saline to remove excess virus, and then implanted in the recipient. He found that there was a high transfection rate, with interstitial fibroblasts expressing the transfected gene most strongly. Initial expression of the reporter gene was high, but dropped off after two weeks to only 7 percent of the original level. The kidney showed only mild levels of cytotoxic lymphocytes, indicating the virus was tolerated reasonably well.

Next, Deelman introduced immunomodulator genes into the virus, and used mice of different strains for donor and recipient. He first tried the gene for interleukin-13 (IL-13), "a potent anti-inflammatory molecule," which reduces proinflammatory cytokines and inhibits macrophage function. As part of the experiment, he compared gene therapy on the kidney alone to injection of the adenovirus intramuscularly into the recipient. "The aim was to see whether this local therapy with IL-3 was as effective as systemic therapy," he said.

Local therapy led to high expression of IL-13 in the kidney at day 8 after transfection, and some reduction of renal damage markers consistent with an immunomodulatory effect. The results were "similar or better than for intramuscular treatment," he said. "Local gene therapy is a feasible alternative to systemic therapy."

The second gene he tried was for 2,3-indoleamine dioxygenase, or IDO. IDO is the rate-limiting enzyme in the catabolism of tryptophan, and high expression depletes tryptophan. The enzyme is abundantly expressed in the placenta during pregnancy, and protects the fetus against rejection. It is also expressed in tumor cells, as a mechanism to escape the immune response. It inhibits naïve T cell proliferation and induces T cell apoptosis, while stimulating regulatory T cells. IDO has been used to prevent acute rejection in diverse organs, including skin, heart, and pancreatic islets, as well as to suppress airway inflammation.

"The aim was to determine whether gene therapy with IDO could have an effect on acute rejection of the transplanted kidney." To test this, both kidneys in the recipient were removed before transplantation, in order to assess the function of the transplanted kidney alone.

The gene was expressed at high levels, and led to a "dramatic reduction" in plasma creatinine versus control, "and a complete normalization of kidney function." Biomarkers of inflammation and renal damage were all lower in the treated mice, and there was less macrophage infiltration and less fibrosis. "This is really quite impressive," Deelman said.

Deelman's group is now examining IDO's potential to reduce chronic transplant dysfunction. Their initial results indicate that at three months, treated mice have no proteinuria, lower blood pressure, and better body weight, compared to controls.

The long-term benefit was not due to continued expression of IDO, since, as before, gene expression was largely absent after two weeks. Instead, Deelman said, early treatment with IDO may protect cells from immune surveillance in the critical early period, or may induce tolerance.

Whether local therapy will prove superior to systemic therapy in humans "remains to be shown," Deelman said.

African Americans, ApoL1, and Kidney Disease

By John F. O'Toole and Leslie A. Bruggeman

Remarkable progress was made in the past year toward understanding the African American predisposition to focal segmental glomerulosclerosis (FSGS) and other nondiabetic kidney diseases. Now taking center stage is the need to understand the biology of ApoL1 and to identify additional genetic or environmental factors that may trigger pathogenicity. Such an understanding is crucial to confirm a causal role of *APOL1* variants and examine potential strategies for early detection and transplantation.

It is well known that African Americans have a higher incidence of chronic kidney disease. In 2008, researchers discovered that a region on chromosome 22 was associated with increased risk for nondiabetic kidney diseases (FSGS, HIVAN, and hypertensive CKD) in individuals of African ancestry (1,2). The search for the causal genetic variant initially focused on *MYH9*, but these studies failed to identify a plausible mechanism for kidney disease pathogenesis. Last year, two groups expanded the search to other genes and identified variants in *APOL1*, which have a stronger statistical association with risk than *MYH9* (3–8) and encode changes to the protein sequence.

APOL1 encodes an apolipoprotein that circulates in the blood bound to HDL particles, and confers resistance to sleeping sickness, an endemic disease in Africa caused by Trypanosome infection (9). Individuals of African ancestry have two common genetic variations in *APOL1* that encode proteins that extend resistance to additional trypanosome species, suggesting a selective advantage is responsible for their frequent occurrence. A single copy of an *APOL1* variant is sufficient for resistance to trypanosomiasis; however, two copies of an *APOL1* variant substantially increase kidney disease risk. Similar to sickle cell disease, there is a survival and evolutionary advantage in being a heterozygote, but a disadvantage in being a homozygote.

The biology responsible for the association of *APOL1* variants with nondiabetic kidney disease is not known. Kidney diseases associated with *APOL1* variants are not simple Mendelian disorders, and many individuals with two risk variants do not develop kidney disease. A second hit appears to be required. A population-based study found these risk variants were absent in European Americans, but 13 percent of African Americans have two risk variants, as well as an increased risk of albuminuria and decreased GFR (10). Although ApoL1 is a circulating protein, ApoL1 localizes to podocytes, proximal tubules, and the vasculature of the kidney (11). It is not clear if ApoL1 is synthesized in these kidney cells or absorbed from the circulation, which has important implications in transplantation. One study reported increased graft loss if the donor kidney carried the *APOL1* risk genotype (12), but recipient genotypes were not determined, and it is premature to exclude donors based on *APOL1* genotype.

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Molecular Mechanisms of Rituximab in the Treatment of Nephrotic Syndrome

By Gentzon Hall and Michelle P. Winn

Watch for more news about the podocyte antigen SMPDL-3b as a potential therapeutic target in the management of nephrotic syndrome in the coming year.

Podocyte injury and death are the *sine qua non* of nephrotic syndrome. Efforts to abate or reverse such injuries through modulation of immunologic and neurohormonal pathways have led to great advances in the management of nephrotic syndrome, but current therapies lack specificity. The good news is there's a new study that sheds light on a possible therapeutic target.

In recent years, rituximab has been the focus of considerable interest as an alternative therapy in the treatment of nephrotic syndrome (1). Rituximab is a chimeric mouse-human anti-CD20 monoclonal antibody that exerts its targeted biological effects through binding to the B-cell surface ligand CD20 to induce antiproliferative and proapoptotic signaling (2). Though no clear mechanism of B-cell-mediated podocyte injury has been identified, the recent discovery of sphingomyelin phosphodiesterase acid-like 3b (SMPDL-3b) as an "off-target" podocyte antigen recognized by rituximab has provided exciting new insights into the molecular mechanisms of rituximab(3, 4).

Little is known about SMPDL-3b or its biological relevance in podocytes, but this 455–amino acid protein of the acid sphingomyelinase family is suspected to facilitate the regulation of ligand-induced ceramide signaling, actin cytoskeletal dynamics, and cell viability. In a study of 41 pediatric kidney transplant recipients at high risk for recurrence of focal segmental glomerular sclerosis (FSGS), Fornoni and colleagues examined the interplay of rituximab with SMPDL-3b(4). The results demonstrate SMPDL-3b as a highly expressed podocyte antigen that is functionally linked to the maintenance of the podocyte actin cytoskeleton, as well as podocyte viability.

With depletion of SMPDL-3b expression, there is disruption of the podocyte actin cytoskeleton leading to podocyte apoptosis and recurrence of FSGS. When added to cultured human podocytes, rituximab binds to SMPDL-3b and preserves its ability to maintain podocyte viability. Recurrence of FSGS was reduced when rituximab was given to these high risk transplant recipients.

We expect that further work will help unravel the complexity of the intracellular signaling pathways that influence podocyte function and viability.

Gentzon Hall, MD, PhD, and Michelle P. Winn, MD, are affiliated with the Duke University Medical Center, Department of Medicine, Division of Nephrology, Center for Human Genetics, in Durham.

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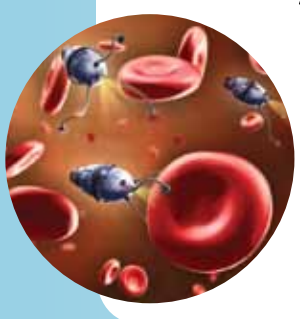
Nanotechnology



The next big thing in medicine may be small. Nanomaterials have moved beyond the laboratory, where they still play an expanding role, and into drug delivery and diagnostic systems. A symposium at Kidney Week 2011 explored these novel materials, including their potential use in a variety of conditions. However, like all advances, nanomedicine has a dark side. Most of these tiny molecules contain metals, and papers published in the past year have demonstrated potential nephrotoxicity in vitro. Other issues with improving tissue delivery and eventual elimination from the body remain as well.

Mobile Technology

Access 24/7 is not just for nephrologists but for information. The Internet remains huge, but the world often uses it from phones and other mobile devices. In addition to the usual range of information delivery services, one new player recently debuted. Doximity, a creation of Jeff Tangney who helped bring Epocrates to the world, wants to be LinkedIn for doctors. The free app lets one join colleagues based on specialty, geography, or common training backgrounds. Location-based services allow search for facilities and pharmacies using a variety of criteria, and a tailored news delivery service is included. The app also has two HIPAA-compliant services for texting between physicians and iRounds, a discussion board for cases and other issues.

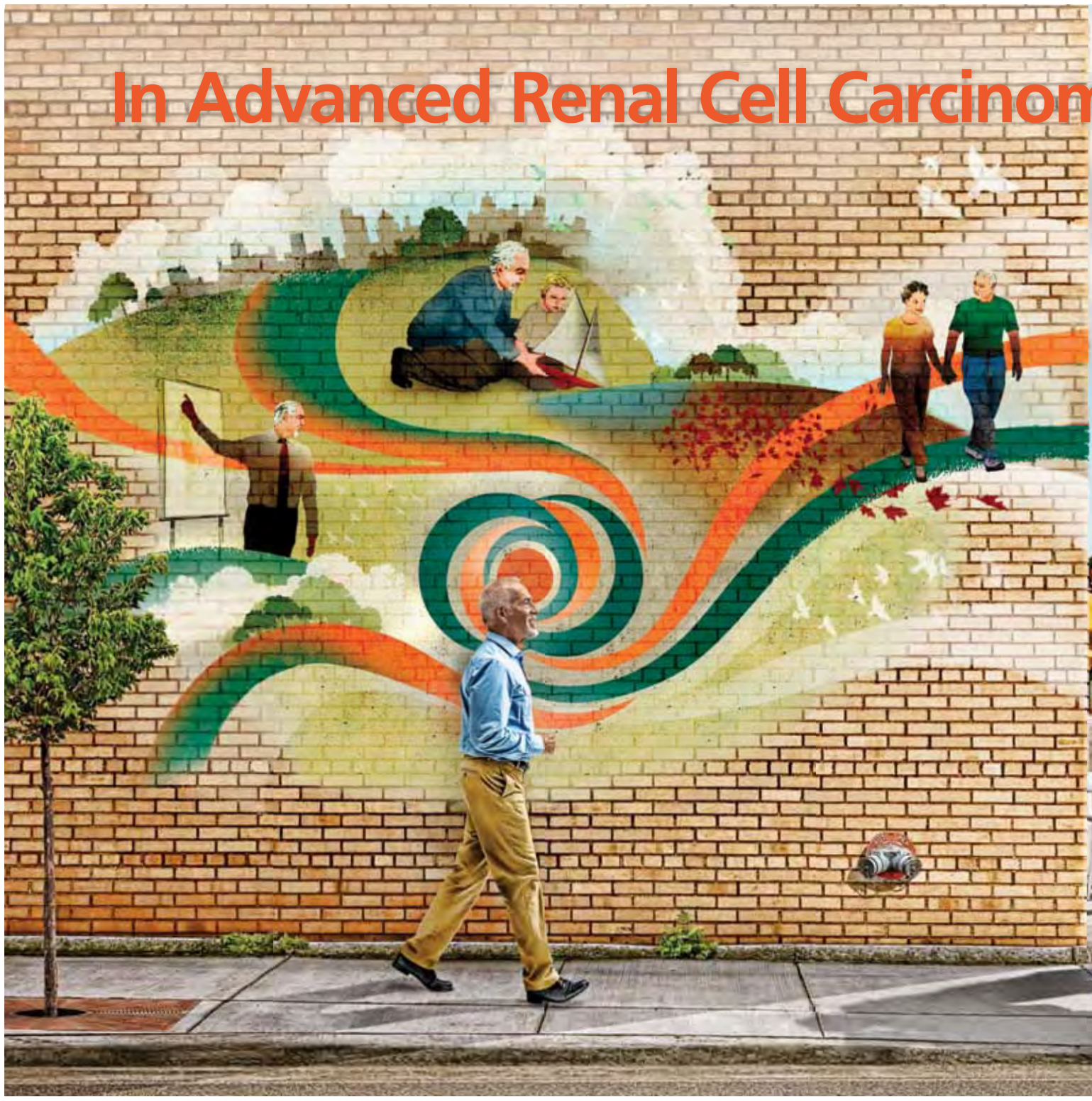
Top 10 Reasons ACOs are Important to the Nephrology Community in 2012

The Medicare Accountable Care Organization (ACO) program is officially launching in 2012. Medicare estimates that between 50 and 270 ACOs will form in the first three years of the program, assuming responsibility for the care of 2 million Medicare beneficiaries. Here are 10 reasons why it is imperative that the nephrology community understand and influence the ACO program in 2012:

1. Significant portions of the Affordable Care Act—which authorized the ACO program—may be on the chopping block, especially if Democrats fail to maintain control of the White House in the 2012 elections. However, the ACO program was one of the few components of the Affordable Care Act to enjoy bipartisan support, and it will have the advantage of already being underway. Nothing is certain in Washington these days, but the ACO program stands a better chance at survival than a number of other Affordable Care Act provisions.
2. ACOs will begin to operate as of Sunday, April 1, 2012. The program is no longer on the theoretical level, but an imminent reality within the Medicare payment system.
3. ACOs are not the only new care delivery model being considered by policymakers.The Centers for Medicare and Medicaid Innovation is designed specifically to test alternative care and payment systems. The first ACOs will almost inevitably yield valuable lessons for other care delivery models to be tested in the future, potentially including disease- or specialty-specific care delivery models.
4. Patients with chronic kidney disease (CKD), end stage renal disease (ESRD), and kidney transplants are eligible to be attributed to ACOs based on their utilization of primary care services.
5. ACOs have the potential to improve the quality of care for patients with CKD. The ACO model could provide incentives to better coordinate care for advancing CKD patients with kidney professionals, preparing patients for dialysis or other renal replacement therapy options more efficiently than current care delivery systems.
6. An ACO's ability to share in savings derived from providing more efficient care than providers under the traditional fee-for-service model is predicated on the ACO achieving 33 quality measures. Several of these quality measures are directly contraindicated for patients with late-stage kidney disease. For example, it may not be appropriate to give a mammogram to a dialysis patient with a limited life expectancy, especially given the risk of a false positive due to the high prevalence of benign breast calcifications in patients with late stage kidney disease. How primary care providers—and nephrologists—can reconcile this conflict remains to be seen, although it will be crucial for the nephrology community to play a leading role.
7. It remains unclear how or if the ACO quality metrics and other mandates, such as individual care plans, will interface with (or duplicate) existing requirements under the ESRD Quality Incentive Program (QIP) or Conditions for Coverage. (For more information about the QIP, please visit ASN's public policy page.)
8. Nephrologists and nephrology practices are eligible to join ACOs. Under CMS' step-wise attribution policy to ACOs (see November *Kidney News* Policy Update for details) nephrologists who join an ACO could have patients directly attributed to them. The potential for improving care for patients with CKD is great….though the potential for unintended consequences for patients on dialysis is not unforeseeable, given the 33 ACO quality metrics. The ASN ACO Task Force will examine the prospective pros and cons for the nephrology community in more detail its upcoming Q&A series.
9. The Sustainable Growth Rate Formula (SGR) is set to kick in a 30 percent reduction in physician payments in 2012. Given the approximately $300 billion cost of repealing the SGR, the medical community will likely have to broker a compromise. A demonstration period of numerous alternative payment models—including ACOs—leading to phase-out of the SGR is one potential compromise being discussed in Washington.
10. Today's medical students and nephrology trainees face a very different, and fast-changing, landscape than the previous generation. In order to attract and retain the highest caliber students to nephrology, the specialty must articulate how it fits in with the changing payment and care delivery systems.

The ASN ACO Task Force is developing resources to help nephrologists understand the implications of ACOs for their patients and practices, including a forthcoming series of Q&As in *Kidney News*. More information on ACOs and nephrology is also available to view online via ASN Kidney Week On Demand, highlighting the two Kidney Week sessions focused on ACOs and other new care delivery models.

In Advanced Renal Cell Carcinoma...



Indication

VOTRIENT is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

Important Safety Information

WARNING: HEPATOTOXICITY
Severe and fatal hepatotoxicity has been observed in clinical studies. Monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended. See "Warnings and Precautions," Section 5.1, in complete Prescribing Information.

- **Hepatic Effects:** Patients with pre-existing hepatic impairment should use VOTRIENT with caution. Treatment with VOTRIENT is not recommended in patients with severe hepatic impairment. Increases in serum transaminase levels (ALT, AST) and bilirubin were observed. Severe and fatal hepatotoxicity has occurred. Transaminase elevations occur early in the course of treatment (92.5% of all transaminase elevations of any grade occurred in the first 18 weeks). Before the initiation of treatment and regularly during treatment, **monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended**.
- **QT Prolongation and Torsades de Pointes:** Prolonged QT intervals and arrhythmias, including torsades de pointes, have been observed with VOTRIENT. Use with caution in patients at higher risk of developing QT interval prolongation, in patients taking antiarrhythmics or other medications that may prolong QT interval, and those with relevant pre-existing cardiac disease. Baseline and periodic monitoring of electrocardiograms and maintenance of electrolytes within the normal range should be performed.
- **Hemorrhagic Events:** Fatal hemorrhagic events have been reported (all Grades [16%] and Grades 3 to 5 [2%]). VOTRIENT has not been studied in patients who have a history of hemoptysis, cerebral, or clinically significant gastrointestinal hemorrhage in the past 6 months and should not be used in those patients.
- **Arterial Thrombotic Events:** Arterial thrombotic events have been observed and can be fatal. In clinical RCC studies of VOTRIENT, myocardial infarction, angina, ischemic stroke, and transient ischemic attack (all Grades [3%] and Grades 3 to 5 [2%]) were observed. Use with caution in patients who are at increased risk for these events.
- **Gastrointestinal Perforation and Fistula:** Gastrointestinal perforation or fistula has occurred. Fatal perforation events have occurred. Use with caution in patients at risk for gastrointestinal perforation or fistula. Monitor for symptoms of gastrointestinal perforation or fistula.
- **Hypertension:** Hypertension, including hypertensive crisis, has been observed. Blood pressure should be well-controlled prior to initiating VOTRIENT. Monitor for hypertension and treat as needed. Hypertension was observed in 47% of patients with RCC treated with VOTRIENT. Hypertension occurs early in the course of treatment (39% of cases occurred by Day 9 and 88% of cases occurred in the first 18 weeks). In the case of persistent hypertension despite anti-hypertensive therapy, the dose of VOTRIENT may be reduced. VOTRIENT should be discontinued if there is evidence of hypertensive crisis or if hypertension is severe and persistent despite

Move Forward With VOTRIENT

In a phase 3, randomized, double-blind, placebo-controlled trial, VOTRIENT provided significant improvement in progression-free survival (PFS) in both treatment-naïve and cytokine-pretreated patients with advanced RCC[1,2]

All patients
9.2 months
(95% CI, 7.4-12.9)
overall median PFS with VOTRIENT (n=290) vs **4.2 months** (95% CI, 2.8-4.2) with placebo (n=145) (*P*<0.001)[1,3]

Treatment-naïve patients
11.1 months
(95% CI, 7.4-14.8)
median PFS with VOTRIENT (n=155) vs **2.8 months** (95% CI, 1.9-5.6) with placebo (n=78) (*P*<0.001)[1,3]

Cytokine-pretreated patients
7.4 months
(95% CI, 5.6-12.9)
median PFS with VOTRIENT (n=135) vs **4.2 months** (95% CI, 2.8-5.6) with placebo (n=67) (*P*<0.001)[1,3]

NCCN Guidelines® Category 1 recommendation[4]

- As a first-line therapy for relapsed or Stage IV unresectable RCC of predominant clear cell histology . These Guidelines also include therapies other than VOTRIENT as first-line treatment options

WARNING: HEPATOTOXICITY
Severe and fatal hepatotoxicity has been observed in clinical studies. Monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended.
See "Warnings and Precautions," Section 5.1, in complete Prescribing Information.

VOTRIENT: Safety Profile Summary[1]

- Most common adverse events observed with VOTRIENT were diarrhea, hypertension, hair color changes (depigmentation), nausea, anorexia, and vomiting
  — Grade 3/4 fatigue occurred in 2% of patients; all grades, 19% of patients
  — Grade 3/4 asthenia occurred in 3% of patients; all grades, 14% of patients
- For any individual adverse reaction in the VOTRIENT arm, the rate of Grade 3/4 adverse events is ≤4%

Most common laboratory abnormalities were ALT and AST increases[1]

- Grade 3 ALT increases occurred in 10% of patients; grade 4, 2% of patients
- In clinical trials, 92.5% of all transaminase elevations of any grade occurred in the first 18 weeks of treatment with VOTRIENT
- Monitor serum liver tests before initiation of treatment with VOTRIENT and at least once every 4 weeks for at least the first 4 months of treatment or as clinically indicated. Periodic monitoring should then continue after this time period

Votrient™
pazopanib tablets (200 mg)

anti-hypertensive therapy and dose reduction of VOTRIENT.

- **Wound Healing:** VOTRIENT may impair wound healing. Temporary interruption of therapy with VOTRIENT is recommended in patients undergoing surgical procedures. VOTRIENT should be discontinued in patients with wound dehiscence.
- **Hypothyroidism:** Hypothyroidism was reported as an adverse reaction in 26/586 (4%). Monitoring of thyroid function tests is recommended.
- **Proteinuria:** Monitor urine protein. Proteinuria was reported in 44/586 (8%) (Grade 3, 5/586 [<1%] and Grade 4, 1/586 [<1%]). Baseline and periodic urinalysis during treatment is recommended. Discontinue for Grade 4 proteinuria.
- **Pregnancy Category D:** VOTRIENT can cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant while taking VOTRIENT.
- **Drug Interactions:** CYP3A4 Inhibitors (eg, ketoconazole, ritonavir, clarithromycin): Avoid use of strong inhibitors. Consider dose reduction of VOTRIENT when administered with strong CYP3A4 inhibitors.

  CYP3A4 Inducers (such as rifampin): Consider an alternate concomitant medication with no or minimal enzyme induction potential or avoid VOTRIENT.

  CYP Substrates: Concomitant use of VOTRIENT with agents with narrow therapeutic windows that are metabolized by CYP3A4, CYP2D6, or CYP2C8 is not recommended.

- **Adverse Reactions:** The most common adverse reactions (>20%) for VOTRIENT versus placebo were diarrhea (52% vs. 9%), hypertension (40% vs. 10%), hair color changes (depigmentation) (38% vs. 3%), nausea (26% vs. 9%), anorexia (22% vs. 10%), and vomiting (21% vs. 8%).

  Laboratory abnormalities occurring in >10% of patients and more commonly (≥5%) in the VOTRIENT arm versus placebo included increases in ALT (53% vs. 22%), AST (53% vs. 19%), glucose (41% vs. 33%), and total bilirubin (36% vs. 10%); decreases in phosphorus (34% vs. 11%), sodium (31% vs. 24%), magnesium (26% vs. 14%), and glucose (17% vs. 3%); and leukopenia (37% vs. 6%), neutropenia (34% vs. 6%), thrombocytopenia (32% vs. 5%), and lymphocytopenia (31% vs. 24%).

  VOTRIENT has been associated with cardiac dysfunction (such as a decrease in ejection fraction and congestive heart failure) in patients with various cancer types, including RCC. In the overall safety population for RCC (N=586), cardiac dysfunction was observed in 4/586 patients (<1%).

Please see Brief Summary of Prescribing Information on adjacent pages.

References: 1. VOTRIENT Prescribing Information. Research Triangle Park, NC: GlaxoSmithKline; 2011. **2.** Sternberg CN, et al. *J Clin Oncol.* 2010;28(6):1061–1068. **3.** Data on file, GlaxoSmithKline. **4.** Referenced with permission from The NCCN Clinical Practice Guidelines in Oncology® for Kidney Cancer V.1.2012. © National Comprehensive Cancer Network, Inc 2011. All rights reserved. Accessed November 17, 2011. To view the most recent and complete version of the guideline, go online to www.nccn.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

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GlaxoSmithKline
Oncology

Transplant Disparities in Kids

Even children can face considerable inequities when it comes to receiving transplants.

This message was driven home in a recent analysis of data from the U.S. Renal Data System from 2000 to 2008 that revealed that the average annual rate of preemptive transplantation was higher among white children with kidney failure than among those who were Hispanic and black. Racial differences were also evident in the type of preemptive transplants children received, where more white patients had living donors (78.8 percent), compared with Hispanics (57.3 percent) and blacks (48.8 percent). Hispanics had a 50 percent and blacks a 56 percent lower rate of preemptive transplants than whites. Differences in the incidence of preemptive transplantation were unexplained by socioeconomic status, as determined by neighborhood poverty and health insurance.

"Among pediatric kidney disease patients in the United States, white patients have a significantly higher rate of getting a kidney transplant without ever starting dialysis compared to blacks and Hispanics," said Emory University's Rachel Patzer, PhD, who co-authored the study and presented it at ASN's Kidney Week. "The reasons for this racial disparity are not entirely clear, but could be due to lower access to health care among minority patients," she added.

One potential explanation could be that children in underrepresented minority groups may have less access to care, noted ASN's immediate past president, Joseph Bonventre, MD, PhD. "It is important to raise the awareness of kidney disease in children among general pediatricians so that all children are evaluated and kidney disease can be picked up early enough so that appropriate management can be brought to bear," he said.

Patzer was also part of a research team that examined racial differences in deaths among children with kidney failure. The study included all kidney failure patients younger than 21 years of age who went on dialysis between January 2000 and September 2008 and did not receive a transplant during the study, which ended in September 2009. The investigators censored patients at death or end of follow-up and excluded patients who received a transplant. They considered neighborhood poverty and health insurance as measures of socioeconomic status.

Among 8146 pediatric kidney failure patients in the study, 896 (9.7 percent) died, and a greater proportion of those who died were black.

"When a child develops end stage kidney disease, their best chance for survival and a good quality of life is to receive a kidney transplant, compared with staying on dialysis. Sadly, some children die before they ever receive a transplant," said first author Sandra Amaral, MD, also of Emory University.

The effect of race on death was significantly modified by health insurance. Blacks with no health insurance had a 59 percent greater rate of death after developing kidney failure compared with whites, while Hispanics had a significantly lower rate of death compared with the other racial groups regardless of insurance status. Amaral noted that more studies are needed to understand why these differences occur.

"Raising public awareness of kidney disease in both pediatric as well as adult populations and alerting our primary care providers to the signs of early kidney disease may go far to establish a diagnosis at an earlier stage in all racial groups and ultimately result in better outcomes for our patients," Bonventre said.

Journal View

Inflammatory Markers May Predict CKD Risk

Elevated levels of several markers of inflammation predict an increased long-term risk of chronic kidney disease (CKD), reports a study in the *American Journal of Kidney Diseases*.

The researchers analyzed data from a predominantly white population of patients enrolled in a prospective study of CKD risk factors. Up to 4926 participants were followed up for 15 years. Levels of inflammatory markers—high-sensitivity C-reactive protein, tumor necrosis factor-α receptor 2 (TNF-αR2), white blood cell count, and interleukin-6—were measured in stored blood samples. Associations with CKD were examined in cross-sectional and longitudinal analyses.

All four inflammatory markers were associated with a higher prevalence of CKD at baseline. On longitudinal analysis of participants free of CKD at baseline, all markers except for C-reactive protein were associated with incident CKD. Hazard ratios, comparing the highest with the lowest tertiles of biomarker levels, were 2.10 for TNF-αR2, 1.90 for white blood cell count, and 1.45 for interleukin-6. The associations were "relatively robust" on adjustment for confounders, and remained significant on analyses using different definitions of CKD.

Animal experiments suggest that inflammatory processes play an important role in the development of kidney disease. The new study identifies several inflammatory biomarkers associated with prevalent and incident CKD in a general population sample. If the findings are borne out by future studies, measuring TNF-αR2, white blood cells, and interleukin-6 might provide a new approach to identifying patients at high risk of CKD [Shankar A, et al: Markers of inflammation predict the long-term risk of developing chronic kidney disease: a population-based cohort study. *Kidney Int* 2011; 80:1231–1238].

vomiting. The data described below reflect the safety profile of VOTRIENT in 290 RCC patients who participated in a randomized, double-blind, placebo-controlled study *[see Clinical Studies (14) of full prescribing information]*. The median duration of treatment was 7.4 months (range 0 to 23) for patients who received VOTRIENT and 3.8 months (range 0 to 22) for the placebo arm. Forty-two percent (42%) of patients on VOTRIENT required a dose interruption. Thirty-six percent (36%) of patients on VOTRIENT were dose reduced. Table 1 presents the most common adverse reactions occurring in ≥10% of patients who received VOTRIENT.

Table 1. Adverse Reactions Occurring in ≥10% of Patients who Received VOTRIENT

	VOTRIENT (N = 290)			Placebo (N = 145)		
	All Grades[a]	Grade 3	Grade 4	All Grades[a]	Grade 3	Grade 4
Adverse Reactions	%	%	%	%	%	%
Diarrhea	52	3	<1	9	<1	0
Hypertension	40	4	0	10	<1	0
Hair color changes	38	<1	0	3	0	0
Nausea	26	<1	0	9	0	0
Anorexia	22	2	0	10	<1	0
Vomiting	21	2	<1	8	2	0
Fatigue	19	2	0	8	1	1
Asthenia	14	3	0	8	0	0
Abdominal pain	11	2	0	1	0	0
Headache	10	0	0	5	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

Other adverse reactions observed more commonly in patients treated with VOTRIENT than placebo and that occurred in <10% (any grade) were alopecia (8% versus <1%), chest pain (5% versus 1%), dysgeusia (altered taste) (8% versus <1%), dyspepsia (5% versus <1%), facial edema (1% versus 0%), palmar-plantar erythrodysesthesia (hand-foot syndrome) (6% versus <1%), proteinuria (9% versus 0%), rash (8% versus 3%), skin depigmentation (3% versus 0%), and weight decreased (9% versus 3%). Table 2 presents the most common laboratory abnormalities occurring in >10% of patients who received VOTRIENT and more commonly (≥5%) in patients who received VOTRIENT versus placebo.

Table 2. Selected Laboratory Abnormalities Occurring in >10% of Patients who Received VOTRIENT and More Commonly (≥5%) in Patients who Received VOTRIENT Versus Placebo

	VOTRIENT (N = 290)			Placebo (N = 145)		
	All Grades[a]	Grade 3	Grade 4	All Grades[a]	Grade 3	Grade 4
Parameters	%	%	%	%	%	%
Hematologic						
Leukopenia	37	0	0	6	0	0
Neutropenia	34	1	<1	6	0	0
Thrombocytopenia	32	<1	<1	5	0	<1
Lymphocytopenia	31	4	<1	24	1	0
Chemistry						
ALT increased	53	10	2	22	1	0
AST increased	53	7	<1	19	<1	0
Glucose increased	41	<1	0	33	1	0
Total bilirubin increased	36	3	<1	10	1	<1
Phosphorus decreased	34	4	0	11	0	0
Sodium decreased	31	4	1	24	4	0
Magnesium decreased	26	<1	1	14	0	0
Glucose decreased	17	0	<1	3	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

Hepatic Toxicity: In a controlled clinical study with VOTRIENT for the treatment of RCC, ALT >3 X ULN was reported in 18% and 3% of the VOTRIENT and placebo groups, respectively. ALT >10 X ULN was reported in 4% of patients who received VOTRIENT and in <1% of patients who received placebo. Concurrent elevation in ALT >3 X ULN and bilirubin >2 X ULN in the absence of significant alkaline phosphatase >3 X ULN occurred in 5/290 (2%) of patients on VOTRIENT and 2/145 (1%) on placebo. *[See Dosage and Administration (2.2) of full prescribing information and Warnings and Precautions (5.1).]* **Hypertension:** In a controlled clinical study with VOTRIENT for the treatment of RCC, 115/290 patients (40%) receiving VOTRIENT compared with 15/145 patients (10%) on placebo experienced hypertension. Grade 3 hypertension was reported in 13/290 patients (4%) receiving VOTRIENT compared with 1/145 patients (<1%) on placebo. The majority of cases of hypertension were manageable with anti-hypertensive agents or dose reductions with 2/290 patients (<1%) permanently discontinuing treatment with VOTRIENT because of hypertension. VOTRIENT has been associated with hypertensive crisis in patients with various cancer types including RCC. In the overall safety population for RCC (N = 586), one patient had hypertensive crisis on VOTRIENT. *[See Warnings and Precautions (5.6).]* **QT Prolongation and Torsades de Pointes:** In a controlled clinical study with VOTRIENT, QT prolongation (≥500 msec) was identified on routine electrocardiogram monitoring in 3/290 (1%) of patients treated with VOTRIENT compared with no patients on placebo. Torsades de pointes was reported in 2/586 (<1%) patients treated with VOTRIENT in the RCC studies. *[See Warnings and Precautions (5.2).]* **Arterial Thrombotic Events:** In a controlled clinical study with VOTRIENT, the incidences of arterial thrombotic events such as myocardial infarction/ischemia [5/290 (2%)], cerebral vascular accident [1/290 (<1%)], and transient ischemic attack [4/290 (1%)] were higher in patients treated with VOTRIENT compared to the placebo arm (0/145 for each event). *[See Warnings and Precautions (5.4).]* **Hemorrhagic Events:** In a controlled clinical study with VOTRIENT, 37/290 patients (13%) treated with VOTRIENT and 7/145 patients (5%) on placebo experienced at least 1 hemorrhagic event. The most common hemorrhagic events in the patients treated with VOTRIENT were hematuria (4%), epistaxis (2%), hemoptysis (2%), and rectal hemorrhage (1%). Nine (9/37) patients treated with VOTRIENT who had hemorrhagic events experienced serious events including pulmonary, gastrointestinal, and genitourinary hemorrhage. Four (4/290) (1%) patients treated with VOTRIENT died from hemorrhage compared with no (0/145) (0%) patients on placebo. *[See Warnings and Precautions (5.3).]* In the overall safety population in RCC (N = 586), cerebral/intracranial hemorrhage was observed in 2/586 (<1%) patients treated with VOTRIENT. **Hypothyroidism:** In a controlled clinical study with VOTRIENT, more patients had a shift from thyroid stimulating hormone (TSH) within the normal range at baseline to above the normal range at any post-baseline visit in VOTRIENT compared with the placebo arm (27% compared with 5%, respectively). Hypothyroidism was reported as an adverse reaction in 19 patients (7%) treated with VOTRIENT and no patients (0%) in the placebo arm. *[See Warnings and Precautions (5.8).]* **Diarrhea:** Diarrhea occurred frequently and was predominantly mild to moderate in severity. Patients should be advised how to manage mild diarrhea and to notify their healthcare provider if moderate to severe diarrhea occurs so appropriate management can be implemented to minimize its impact. **Proteinuria:** In the controlled clinical study with VOTRIENT, proteinuria has been reported as an adverse reaction in 27 patients (9%) treated with VOTRIENT. In 2 patients, proteinuria led to discontinuation of treatment with VOTRIENT. *[See Warnings and Precautions (5.9).]* **Lipase Elevations:** In a single-arm clinical study, increases in lipase values were observed for 48/181 patients (27%). Elevations in lipase as an adverse reaction were reported for 10 patients (4%) and were Grade 3 for 6 patients and Grade 4 for 1 patient. In clinical RCC studies of VOTRIENT, clinical pancreatitis was observed in 4/586 patients (<1%). **Cardiac Dysfunction:** Pazopanib has been associated with cardiac dysfunction (such as a decrease in ejection fraction and congestive heart failure) in patients with various cancer types, including RCC. In the overall safety population for RCC (N = 586), cardiac dysfunction was observed in 4/586 patients (<1%).

7 DRUG INTERACTIONS

7.1 Drugs That Inhibit or Induce Cytochrome P450 3A4 Enzymes

In vitro studies suggested that the oxidative metabolism of pazopanib in human liver microsomes is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8. Therefore, inhibitors and inducers of CYP3A4 may alter the metabolism of pazopanib. **CYP3A4 Inhibitors:** Coadministration of pazopanib with strong inhibitors of CYP3A4 (e.g., ketoconazole, ritonavir, clarithromycin) may increase pazopanib concentrations. A dose reduction for VOTRIENT should be considered when it must be coadministered with strong CYP3A4 inhibitors *[see Dosage and Administration (2.2)]*. Grapefruit juice should be avoided as it inhibits CYP3A4 activity and may also increase plasma concentrations of pazopanib. **CYP3A4 Inducers:** CYP3A4 inducers such as rifampin may decrease plasma pazopanib concentrations. VOTRIENT should not be used if chronic use of strong CYP3A4 inducers can not be avoided *[see Dosage and Administration (2.2)]*.

New Data on Cancer Risk after Organ Transplantation

Patients with kidney or other solid organ transpalants are at increased risk of a wide range of cancers, reports a study in *The Journal of the American Medical Association*.

The researchers used linked cancer registries to analyze patterns of cancer risk after organ transplantation. The analysis included data on 175,732 solid organ transplant recipients, approximately 58 percent of whom received kidney transplants. The rest received liver (22 percent), heart (10 percent), and lung (4 percent) transplants.

The overall incidence of cancer after organ transplant was 1375 per 100,000 person-years, with a standardized incidence ratio (SIR) of 2.0. The increase was seen not only for infection-related cancers such as Kaposi sarcoma and anal cancer; but also for cancers with no known link to infection, such as melanoma, thyroid cancer, and lip cancer. The most common cancers showing excess risk were non-Hodgkin lymphoma, SIR 7.54; lung cancer, SIR 1.97; liver cancer, SIR 11.56; and kidney cancer, SIR 4.65.

Lung cancer risk was highest in lung transplant recipients, but was also increased for kidney recipients: SIR 1.46. The risk of kidney cancer was highest for kidney transplant recipients, SIR 6.66, with an initial peak in the first year and a second peak during years 4 to 15. Kidney cancer risk was also increased for liver and heart recipients: SIR 1.80 and 2.90, respectively.

The results show an increased risk of a wide range of cancers—including cancers apparently unrelated to infection—in kidney, liver, heart, and lung recipients. Especially with improvement in long-term survival rates, new approaches to cancer prevention and early detection after organ transplantation are needed [Engels EA, et al: Spectrum of cancer risk among US solid organ transplant recipients. *JAMA* 2011; 306: 1891–1901].

Policy Update

ASN Supports CDC Initiative to Develop Electronic Death Certificate

Recognizing the value to a comprehensive, detailed electronic database regarding all causes of death nationwide, the Centers for Disease Control and Prevention (CDC) recently initiated development of an electronic death certificate that will eventually be used nationwide. The CDC is currently pilot testing the program.

Acknowledging the role of kidney disease in many deaths every year, the CDC asked ASN to help in their effort during ASN Kidney Week 2011. More than 30 members of ASN advisory groups volunteered their time at Kidney Week to participate in a one-on-one interview with the CDC to test the program, whose working title is "TurboDeath."

The goal of TurboDeath is to develop a "next generation" collection method for mortality records. The current Electronic Death Registration System model (which essentially reproduces the paper death certificate form in electronic media) would be replaced with an interview style format modeled on the popular "TurboTax" program. By allowing form completers to focus exclusively on providing accurate medical knowledge information, rather than on boxes and placement in a form, TurboDeath's objective is to improve the quality and accuracy of the collected information. In conjunction with modern applications and tools such as tablets, it is hoped that the product will reduce the effort and time required for delivering quality medical mortality information.

"A nationwide electronic death certificate would significantly increase the accuracy and comprehensiveness of mortality data, with enormous benefit from a research perspective," said Public Policy Board Chair Thomas H. Hostetter, MD. "I am gratified that ASN is a strong contributor to the development of this important public health initiative."

"I would like to thank you and ASN for the opportunity you provided us to demonstrate TurboDeath to your members," said Charles Sirc, MD, chief of the CDC Mortality Medical Classification Branch. "The physicians who took the time to come to the demonstration were extremely generous with their time and provided excellent comments and suggestions. It was an extremely successful demonstration."

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Up in Space: *Medicine off the Earth" was the topic of a lecture by Jonathan B. Clark at Kidney Week 2011. Clark is assistant professor of neurology and space medicine at Baylor College of Medicine and Center for Space Medicine. He is also clinical assistant professor at the University of Texas Medical Branch. He worked at NASA as a space shuttle crew surgeon from 1997 to 2005.*

Here ASN Past President Joseph V. Bonventre interviews Dr. Clark about the health effects of space and the space program's potential long-term benefits for humans.

For the full interview, see the Kidney News online app.

Dr. Bonventre: In your talk you mentioned issues with bone loss and kidney stones. Could you talk a little about bone loss, the release of calcium, and the formation of stones?

Dr. Clark: Astronauts undergo rigorous physical screening. They do not have a history of kidney stones when they come into the astronaut program. In the astronaut corps of approximately 300 astronauts, 12 have had kidney stones, and two have had repeated kidney stones. Many of those stones developed in the postflight period. Bodies adapt to the absence of gravity by releasing calcium, specifically from the weight-bearing bones. That release of calcium causes hypercalciuria, one of the major risk factors for kidney stones. In the 1980s, one of the Russian cosmonauts developed a kidney stone in space.

At that time, the United States was focusing on shorter missions, but the Russians were supporting longer missions and were at greater risk for kidney stone formation. We know that there is a reduction in bone density in space crews at a rate about 10 times greater than the calcium mobilization experienced on earth. We see an increase in calcium in the urine and a decrease in bone density, similar to what is seen in postmenopausal osteoporosis but at a 10 times greater rate. Whereas a postmenopausal woman might lose bone density at a rate of about 1–2 percent per year, those in space lose bone density at a rate of about 1–2 percent per month. Bone loss in patients with spinal cord conditions seems to plateau after about 2.5 years. So far, no one has flown in space for longer than 14 months, and in those missions we have not seen the plateau in bone density loss.

Dr. Bonventre: How much of the bone loss is reversible?

Dr. Clark: Well, bone density goes down as we age. This isn't my area of expertise, but for accelerated bone loss in space, the recovery period is much longer than the loss period. Astronauts will recover bone density, but it may take three times longer to recover the bone density as it took to lose it. We have seen some instances of male crew members who have experienced hip and femoral fractures not due to trauma.

Dr. Bonventre: One of the goals of the space program is to go to Mars. A Mars trip would take about 6 months travel time each way and a year on Mars; is that right?

Dr. Clark: A Mars mission might range from 13 months to 30 months: a 6-month transit period each way and a stay of either 1 month or 1 year. The challenges include minimizing travel time in microgravity and addressing the exposure to radiation in deep space, which is very problematic. Interestingly, some recent studies indicate that radiation also contributes to bone loss, perhaps by an effect on the bone-forming cells in our long bones.

Dr. Bonventre: So bone loss is one problem with that kind of mission. Another would be a medical emergency in deep space. How is NASA preparing for that?

Dr. Clark: Dealing with a medical emergency in space is challenging, even in low earth orbit. We just returned to a six-person crew on the space station; imagine how difficult it would be to take care of a medical emergency with just a three-person crew. Right now the best plan for a Mars mission would be to have a six- or seven-person crew. NASA is evaluating training, equipment, and procedures that would work best in a deep space mission. In addition, the length of time it takes for a signal to be sent back and forth poses challenges. Going to Mars, currently you would experience a time delay of 14–40 minutes for two-way communication, with no ability to get real-time feedback on a medical problem.

Right now we're developing some advanced diagnostic imaging, primarily with the ultrasound machine. Ultrasound has drastically improved; the original ultrasound machine on the space station was like the old-time cart in the cardiology suite—a fairly large machine. Now you can get ultrasound machines the size of midsized laptops that provide real-time feedback. New technologies have been developed that support expeditionary medicine and medicine in austere environments, such as natural disasters in remote locations. It's interesting that so many NASA technologies support life on earth, not just the few people who travel up in space.

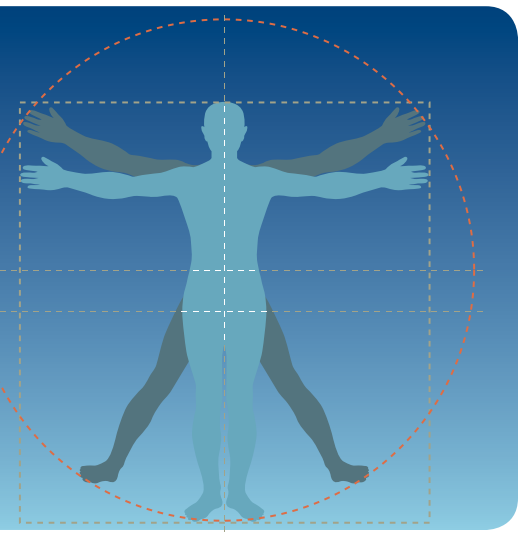
Dr. Bonventre: One other implication of space travel is muscle wasting, both cardiac and skeletal. What are the countermeasures, and can the loss be reversed?

Dr. Clark: The human body is an amazing system. It's very adaptive. In microgravity the body senses that it doesn't need muscles, bones, or a cardiac system as strong as what it requires on earth. The body adapts to the absence of gravity, but this is of course maladaptive for the return to gravity. Adjusting to the absence of gravity, the body dumps excess bone and calcium and reduces skeletal muscle mass. Cardiac muscle mass is lost because the body doesn't need to maintain blood pressure the way it does in a gravity environment. Cardiac echo ultrasounds have shown a reduction in cardiac mass and a reduction in aerobic fitness as measured by cardiac output and heart rate in response to exercise challenge. There has been a huge effort to counteract those degrading systemic effects on the body. Most of the countermeasures involve some form of exercise: to enhance cardiac fitness and to enhance musculoskeletal strength with resistance exercise.

In space station crews, with missions lasting 6–7 months, muscle mass and aerobic capacity in space decline very rapidly: down 20–30 percent compared with normal. This slowly recovers toward the end of the flight, but it is still 10–20 percent from normal. In the first week after a flight, astronauts have the same deficit experienced in space but recover after a month. What we don't know is what the recovery might be for someone who is already in a cardiac-compromised state. This ties into concerns regarding commercial space flight and the likelihood that we'll see people in less than pristine medical shape. Commercial space travelers may have underlying pathologic conditions of any organ system. The majority of early commercial space flights will be suborbital and might last for 5–10 minutes. Space tourists have stayed on the space station for 10–14 days but no longer. We may see commercial flight participants flying for longer periods of time—up to 6 months or longer. The medical communities will be challenged. Making sure a healthy person doesn't decline in capabilities is already a challenge, but what about someone not in the best physical shape, or who has underlying medical conditions?

Dr. Bonventre: You mentioned increased intracranial pressure, exemplified by eye changes in the astronauts. Is that also associated with elevations in systemic blood pressure or other complications? Are there countermeasures in place, especially for longer-term space travel?

Dr. Clark: The problem with increased intracranial pressure has only recently been recognized by NASA. The first case was recognized in 2005, and since then we've had eight cases in 34 crew members. This may represent the gravest concern for human space flight. Some of these people exhibit elevations, even years later, as if their bodies had adapted to this state and



never fully returned to normal. NASA has initiated a massive effort to understand more about this problem, and it encompasses all specialties, including nephrology. For instance, carbonic anhydrase inhibitors, also used to treat mountain sickness and high-altitude cerebral edema, have been used to treat intracranial pressure. Unfortunately, the side effect of that treatment is increased risk of kidney stones—a risk already associated with space flight. We don't understand all aspects of this problem; there is speculation that the choroid plexus is involved, and some of the secretion and absorption phenomena of the brain to wash out contaminants and bring in nutrients may have some similarities to kidney function. I'm interested in connecting with nephrologists, who understand these cellular-level activities and might help us understand more about increased intracranial pressure in space.

Dr. Bonventre: You mentioned waste product recirculation. Are the engineering systems in space efficient in terms of reprocessing waste products?

Dr. Clark: The urine recycler, officially called the water recovery system, was an amazing engineering feat. The water recovery system flew on the space station at the end of 2008, and it enabled the recovery of condensate collected from humid air and from urine. That system uses a lot of advanced technologies, such as filters and molecular sieves, that have allowed the space station to go from a three-person crew to a six-person crew. It was vital to the development of a partially closed loop space habitation. The astronauts weren't just bringing drinking water up and then dumping it overboard; they were recycling and reusing. It's incredibly important to survival in space and to survival on earth. Many places on earth don't have adequate water supplies, so there is a great value in the ability to process nonpotable water so that it meets health standards.

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Detective Nephron

Detective Nephron, world-renowned for expert analytic skills, trains budding physician-detectives on the diagnosis and treatment of kidney diseases. L. O. Henle, a budding nephrologist, presents a new case to the master consultant.

Nephron (angry) My assistant is late today.

L. O. Henle enters the room with excitement.

Nephron What do you want?

Henle I…I have a case for us.

Nephron You are late today.

Henle Hypomagnesemia.

Nephron (with surprise) Excellent. A good case can change my mood.

Henle (prepared) A 65-year-old man was just seen recently for fatigue and muscle weakness and found to have a serum magnesium level of 0.6 mg/dL.

Nephron This should be fun.

Henle (with a curious look) For 3 days they tried giving him magnesium replacements intravenously and via mouth, and it is improving, but they can't figure out the cause.

Nephron (confused) Ahhah! This is going be exciting.

Henle Just some more information, if you allow it, sir.

Nephron Sure—I hope it is the information I am looking for.

Henle He really has no significant medical problems except hypertension and gastric reflux disease. His FeMg was 0.5 percent.

Nephron So it's a gastrointestinal (GI) loss. Why are you bothering me?

Henle He has no diarrhea, and no apparent GI loss can be found. He has no history of alcohol ingestion.

Nephron (very excited) Great job; let's move on. So just because there is no GI loss, it is presumed renal losses? You just told me that the kidney is doing the right thing: the urinary loss of magnesium is very minimal. If I had to guess what the urine magnesium was, it must have been very low.

Henle You are correct.

Nephron Any other electrolyte problems?

Henle (astounded) I am getting to that point. Also, hypokalemia and hypocalcemia.

Nephron (calm) Fascinating!

Henle So far he is not taking any diuretics, he was not aggressively volume expanded and not hypercalcemic, and I don't see anything on his medication list that can cause renal magnesium wasting, like a chemotherapy agent, calcineurin inhibitors, or amphotericin B.

Nephron Ridiculous! Why are you even bothered by those things when the kidney is doing the right thing! This is GI loss to me. Please go back and evaluate his medications, and make sure he is not having any GI losses.

Henle exits, and Detective Nephron resumes drinking his coffee.

Nephron (to himself) Henle seems to be very puzzled by this one. So far, the kidneys are the smarter organ here!

Before Detective Nephron can go get more coffee, Henle returns to th office.

Nephron You're back.

Henle I am puzzled. His magnesium is persistently low, and his repeat urinary FeMg percent level is appropriately low.

Nephron Good!

Henle When we have renal losses, the cause is usually medication, diuretics, certain antibiotics like gentamicin or foscarnet, or primary renal wasting from syndromes. But as you said, it is not a renal cause. He has no diarrhea or pancreatitis, no known or existing malabsorption disease. He has had no known abdominal surgery.

Nephron Great! The magnesium content of upper GI tract secretions is 15 mEq/L compared with 1 mEq/L in the lower tract, so that in general, magnesium depletion due to upper GI tract secretory loss is much more common than that due to lower GI tract disorders. You did some good work. But we still don't have a diagnosis.

Henle Yes, you are correct.

Nephron (confidently) Look at his medication list and his known diagnosis. He has hypertension and gastric reflux. What is he taking?

Henle Metoprolol and omeprazole.

Nephron (chuckling) All right, then!

Henle What?

Nephron Stop the omeprazole, and recheck the magnesium level in a week.

Henle Really?

Nephron Yes, proton pump inhibitors (PPI) can cause hypomagnesemia, especially long-term use. Hypomagnesemia in this patient's range, along with hypocalcemia, has been reported in PPI use. Usually the loss is GI, so the urinary magnesium and calcium are low. Hypomagnesemia is associated with hypocalcemia, and this is due to both decreased parathyroid hormone secretion and parathyroid hormone resistance. Hypomagnesemia-induced kaliuresis leading to hypokalemia can be seen with these patients as well. The urinary calcium and potassium in this patient?

Henle Low and high, respectively. Given the low calcium, his parathyroid hormone was checked, and it is 30 pg/mL.

Nephron So stop the PPI now!

Henle Why does this happen?

Nephron (with a smirk) It is speculated that the drug might interfere with intestinal absorption. Some data say that there might be a renal effect as well. Data from case reports suggest that a renal effect may also contribute. It is possible that the drug interferes with the maximum tubular reabsorption threshold for magnesium.

Henle This is interesting.

Nephron Let me know in a week.

Henle exits, and Detective Nephron starts reading* ASN Kidney News. *A few days later, as the detective is sipping away at his coffee, Henle enters the office.

Nephron Nothing is better than a cup of hot coffee! And a great case!

Henle Once we stopped the PPI and the magnesium, the patient's calcium and potassium all improved slowly. He is being discharged and is asked not to take these agents any more.

Nephron Great work, Henle. Again, my dear apprentice, from a diagnosis of hypomagnesemia, you found the culprit agent. Always, to be a good detective, observe, think, read, and apply. If it doesn't cross your mind, you will never diagnose it. Great case, Henle. The problem is not always in the kidney!

"Detective Nephron" was developed by Kenar Jhaveri, MD, assistant professor of medicine at Hofstra North Shore LIJ School of Medicine. Thanks to Dr. Rimda Wanchoo, division of nephrology, Weill Cornell Medical Center, for editorial assistance.

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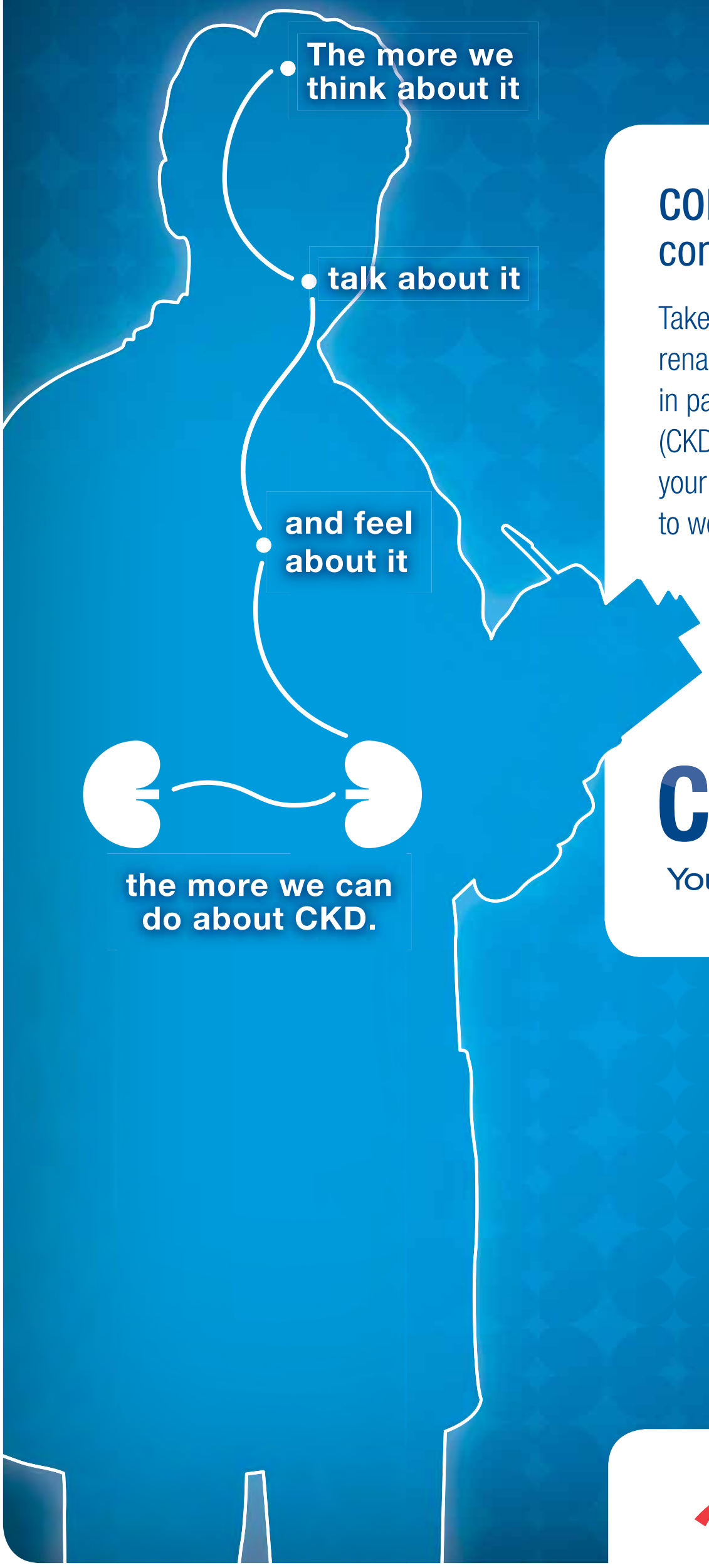

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